PAMIDRONATE AS TREATMENT OF SEVERE HYPERCALCEMIA IN SCFN OF THE NEWBORN: A CASE REPORT

Raiwathy Krishnasamy, Angeline Wan Seng Lian, Nalini M Selvendran

Abstract
Subcutaneous fat necrosis of newborn (SCFN) is an uncommon entity that occurs in neonates who experienced perinatal stress. We report use of pamidronate, to control persistent hypercalcemia in a 5-week-old infant with SCFN not responding to initial treatment. A term male neonate was born by emergency LSCS due to non-reassuring fetal status. Antenatal mother had gestational diabetes mellitus, group B streptococcus carrier and an antenatal scan at 29 weeks detected a fetus with dilated small bowel. Baby was born vigorous but complicated with bowel perforation requiring fluid resuscitation and a bedside glove drain. He underwent laparotomy for small bowel perforation secondary to ileal atresia and required TPN postoperatively. At 1 month of life, he had palpable purplish lumps at his trunk and limbs associated with severe hypercalcemia supporting the diagnosis of subcutaneous fat necrosis. Despite receiving initial treatment of hyperhydration and frusemide for two weeks, the patient's hypercalcemia peaked to 4.11mmol/L. His renal ultrasound showed nephrocalcinosis with renal and bladder calculi. He was given IV Pamidronate. Post single dose of IV Pamidronate, calcium levels reduced ranging 2.2-3 mmol/L and frusemide was discontinued. On discharge he was maintained on low calcium milk. During his first follow up the calcium level remained stable and repeated ultrasound showed resolution of the renal pelvis and bladder calculi with persistence of the medullary nephrocalcinosis. SCFN has a potentially life-threatening complication due to development of severe hypercalcemia. For patients with severe hypercalcemia not responding to hydration, and low calcium intake, pamidronate is an effective and safe treatment. Good supportive management is very important and should be done prior to pamidronate.

Keywords: Subcutaneous fat necrosis of the newborn; hypercalcemia; Pamidronate

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Introduction
Subcortaneous fat necrosis of the newborn (SCFN) is a rare condition that affects newborn who have endured prenatal stress. Although the specific cause of this condition is unknown, it is hypothesised that ischemic damage, hypoxia, or hypothermia are the initial causes. The most serious consequence is hypercalcemia. Prompt diagnosis and treatment is warranted to reduce morbidity and mortality [1]. Till date, few case reports have described the use of intravenous bisphosphonates to treat hypercalcemia associated with SCFN. The effectiveness of a particular pamidronate dosage for hypercalcemia-hypercalciuria in a young newborn has not yet been identified. We describe a case of severe hypercalcemia complicating SCFN in a young infant, who was not responding to hyperhydration, effectively managed with intravenous pamidronate at lower doses than previously described.

Case Presentation
A term male neonate was delivered via emergency caesarean section due to non-reassuring fetal status. The mother was 28 years old primigravida with gestational diabetes mellitus on insulin therapy and a group B streptococcus carrier. The antenatal scan at 29 weeks showed a fetus with a dilated small bowel.

Baby was born vigorous but had a tense dilated abdomen and an abdominal radiograph confirmed bowel perforation necessitating an emergency bedside glove drain. At Day 5 of life, he underwent

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a laparotomy that confirmed a diagnosis of bowel perforation secondary to ileal atresia. He had hypotension during the perioperative period requiring fluid bolus and initiation of inotropes, which was subsequently weaned off and he was extubated by the third day.

Feeding was initiated at Day 3 post operatively and was slowly titrated up, balanced with total parenteral nutrition (TPN). At the 2nd week of life, he was noted to have high calcium levels (2.3-2.7 mmol/L) despite being on low calcium intravenous and oral feeds. At Day 30 of life, he was noticed to have indurated subcutaneous lesions on the back and shoulders which were associated with severe hypercalcemia (3.7-4 mmol/L) and hypertriglyceridemia (2.9-3 mmol/L). The provisional diagnosis of hypercalcemia secondary to subcutaneous fat necrosis was made and patient was referred to paediatric endocrinology. There was no clinical/laboratory evidence of hyperparathyroidism, hypophosphatasia, vitamin D intoxication, malignancy or William syndrome. Paired investigations revealed suppressed PTH level with deficient Vitamin D levels (Table 1).

Despite 2 weeks of aggressive treatment with intravenous hydration of up to 200 ml/kg/day and intravenous diuretics up to 0.5mg/kg thrice a day, he still had severe hypercalcemia with hypercalciuria. Screening for metastatic calcification showed there were presence of bilateral nephrocalcinosis with renal and bladder calculi. Due to severe persistent hypercalcemia complicated with renal calculi, he was treated with low dose IV Pamidronate 0.2mg/kg/dose over 6 hours and corrected calcium levels repeated 6 hours post pamidronate showed the level significantly reduced from 4.11 to 3.48 mmol/L. He developed fever 6 hours post Pamidronate which resolved and there were no other side effects observed. The next day we were able to wean off diuretics, hyperhydration and his calcium levels still remained stable ranging 2.5-3 mmol/L (Table 2). Clinically he remained well and the palpable purplish subcutaneous nodules also regressed within the following week, he was discharged with low calcium formula milk. During his first follow up, calcium level remained stable at 2.5 mmol/L with the repeated ultrasound showed resolution of the renal pelvis and bladder calculi with only persistence of the medullary nephrocalcinosis. Both kidneys were growing each at 5.1-5.5 cm respectively.

Table 1. Initial Laboratory values prior to pamidronate.

<table>
<thead>
<tr>
<th>Lab Test</th>
<th>Result</th>
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<tbody>
<tr>
<td>Calcium</td>
<td>4.11 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.01 mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0.84 mmol/L</td>
</tr>
<tr>
<td>PTH</td>
<td>0.5 pmol/L</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>27 nmol/L</td>
</tr>
<tr>
<td>Urine calcium to creatinine ratio</td>
<td>2.37</td>
</tr>
</tbody>
</table>

Table 2. Follow up calcium levels post pamidronate.

<table>
<thead>
<tr>
<th>Interval Post Pamidronate Administration</th>
<th>Serum Calcium Levels (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-Hours Post</td>
<td>3.48</td>
</tr>
<tr>
<td>Day 1</td>
<td>3.71</td>
</tr>
<tr>
<td>Day 2</td>
<td>2.86</td>
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<tr>
<td>Day 3</td>
<td>2.45</td>
</tr>
<tr>
<td>Day 4</td>
<td>2.42</td>
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<tr>
<td>Day 5</td>
<td>2.2</td>
</tr>
<tr>
<td>Day 14</td>
<td>2.97</td>
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<tr>
<td>Day 21</td>
<td>2.59</td>
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</tbody>
</table>

Table 3. Urinary calcium levels pre and post pamidronate

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Urine Calcium (mmol/L)</td>
<td>8.1</td>
<td>4.0</td>
<td>2.7</td>
<td>2.8</td>
<td>&lt;0.25</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Urine Creatinine (umol/L)</td>
<td>597.6</td>
<td>830.3</td>
<td>403.8</td>
<td>426.3</td>
<td>461.4</td>
<td>579.7</td>
<td>1,023.8</td>
</tr>
<tr>
<td>Urine Ca/Cr</td>
<td>4.8</td>
<td>1.71</td>
<td>2.37</td>
<td>2.33</td>
<td>0.19</td>
<td>0.18</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Discussion

The pathogenesis of hypercalcemia related to SCFN is not completely understood. It has been demonstrated that elevated levels of 1-alpha-hydroxylase exist in the granulomatous cells in SCFN [6]. The 1-alpha-hydroxylase converts the 25-OH vitamin D to 1,25-OH vitamin D which causes calcium release from bones and increases calcium absorption from the gut. There have been other proposed mechanisms which include increased prostaglandin E or parathyroid hormone; however, when levels of those hormones are obtained, they are usually normal. Another postulation includes decreased renal clearance of calcium, thus leading to elevated serum calcium levels [1-4]. Literature review indicates that, over two thirds of patients with SCFN will develop hypercalcemia. Persistent hypercalcemia may then lead to nephrocalcinosis, which may persist for several years without evidence of renal dysfunction. However, the long-term clinical significance of nephrocalcinosis remains uncertain. While nephrocalcinosis is a complication of hypercalcemia and hypercalciuria, its clinical significance depends on the etiology.

Preferred initial therapy for hypercalcemia related to SCFN is hyperhydration, although the rate is not clearly defined in literature [1-3, 6-10]. Diet modification has also been used, which includes a low calcium formula. A combination of saline fluid hydration with diuretics is a recognized standard first-line intervention. Other medications used include corticosteroids and diuretics. [10-15]. In the treatment of these patients’ calcitonin can be considered in the acute setting to transiently reduce calcium levels. Its use is limited due to the occurrence of tachyphyaxis [16].

Pamidronate therapy may be considered after consultation with paediatric endocrinology services, if the hypercalcaemia is refractory to conventional therapy. The main effect of pamidronate is to inhibit bone resorption, which results in a decrease in serum calcium. Because it reduces renal calcium load, it does not increase the risk of nephrocalcinosis. When comparing pamidronate to other treatment options, more recent papers have found that it also reduces the length of stay in hospital [7, 8]. The dose and frequency of pamidronate required may need to be titrated according to the age of the patient and the severity of the hypercalcaemia. In a recent review of the use of pamidronate in SCFN – related hypercalcaemia doses used were 0.25 mg/kg/dose to 0.5 mg/kg/dose without major adverse effects. [7, 8]. With the usage of pamidronate, adverse events of the therapy should be monitored such as an acute “flu-phase” reaction with fever, myalgia, bone pain, vomiting and hypocalcaemia [8].

Conclusions

SCFN is a rare and generally benign dermatological diagnosis that causes hypercalcemia in half of those diagnosed. Certain traumatic neonatal events predispose infants to SCFN, though the exact pathogenesis remains unknown. Diagnosis is essentially clinical and a skin biopsy is not needed for its diagnosis. When it is associated with hypercalcemia, treatment involves reduction of calcium and vitamin D in the diet, adequate hydration with saline followed by IV frusemide therapy. In our case the severe hypercalcemia remained refractory to the hydration but responded well to a single low dose pamidronate that proved to be a safe and effective option. Pamidronate was well tolerated in our patient who did not tolerate full oral feeding yet post gut surgery. In addition, our dose was also lower at 0.2mg/kg/dose than previously described. Using pamidronate may obviate the need for therapy with furosemide and corticosteroids. This case demonstrates the role of pamidronate in the treatment of SCFN related hypercalcemia which is resistant to conventional therapy. Collaboration between the treating paediatrician and the paediatric endocrinologist is recommended when considering the use of pamidronate for the treatment of hypercalcemia. The long-term effects of administering pamidronate to neonates are not yet fully understood. Additionally, there are potential short-term effects such as fever, hypocalcaemia, and respiratory distress that may occur in neonates or very young infants. Therefore, it is advisable for the healthcare professionals involved to make a joint decision based on the individual patient’s condition and consider the potential risks and benefits before proceeding with pamidronate treatment.

Abbreviations

SCFN: Subcutaneous Fat Necrosis of The Newborn; TPN: Total Parenteral Nutrition; PTH: Parathyroid Hormone

Ethics approval and consent to participate.

Approved by the National Medical Research Registry.

Consent for publication

Written informed consent was obtained from the patient’s parents for the publication of this case report and images.
**Availability of data and material**
Not applicable.

**Competing interests**
The authors declare that they have no competing interests.

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Not applicable.

**Authors' contributions**
All authors were involved in the clinical care of the patient. All authors read and approved the final manuscript.

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**References**


